Rw

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,836	06/01/2001	Shikha P. Barman	08191-018001	3677

26161 7590 01/25/2005

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/872,836	BARMAN ET AL.
	Examiner	Art Unit
	Dave T Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,21-29,31-34 and 37* is/are pending in the application.

4a) Of the above claim(s) *5 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-16,21-24, 26-29,31-34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/9/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group I claims, claims 1-16, 21-29, 31-34, and 37, and the species of a peptide having a length and sequence that permit it to bind to an MHC class I molecule, the species PEG-DSPE (newly cited in claim 37, which is accepted as an elected species), in the response dated Nov. 2, 2004, is acknowledged.

Claim 5, 25, directed to a non-elected species, has been withdrawn by the examiner.

Claims 1-4. 6-16, 18-24, 26-30, to which the following grounds are applicable, are pending.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-4, 6-7, 9-16, 29, and 37 are rejected under 35 USC 102(e) as being anticipated by Papahasdjopoulos *et al.* (US Pat No. 6,803,053).

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a protein or proteins of interest, and a cationic lipid/co-lipid complex. Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome.

As such, the microparticles of Papahasdjopoulos *et al.* is not encapsulated in a liposome and does not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the fact that so long as the entire complex is physiologically acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Claims 1-4. 6, 7-16, 29, 32-34, and 37, embracing a polymeric microparticle entrapping lipid:nucleic acid complexes, are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahasdjopoulos *et al.* taken with Rolland (US Pat NO. 6,040,295), and further in view of Lusford (US 2002/0182258 A1).

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a protein or proteins of interest, and a cationic lipid/co-lipid complex. Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while

leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome.

As such, the complexes of Papahasdjopoulos *et al.* is not encapsulated in a liposome and does not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the fact that so long as the entire complex is physiologically acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Papahasdjopoulos *et al.* does not teach that the complexes can be further entrapped within polymeric microparticles with a diameter of less than about 100 microns that are used in the prior art to prolong the controlled release and bioavailability

of a nucleic acid plasmid complex, nor does Papahasdjopoulos *et al.* teaches explicitly that an antigenic peptide or protein encoding DNA can be used for delivery and/or expression at a desired targeted tissue such as a vagina or a mucosal tissue.

However, at the time the invention was made, Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations, *e.g.,* those formulated with a carrier or stabilizer such as a cationic polymer (abstract, entire disclosure, particularly column 1 bridging column 2, column 2, second par.. , column 3, last par bridging column 4). An addition of a targeting ligand to the microparticles and/or plasmid is also taught by Rolland so as to enhance the expression of the complexed plasmid vectors at a desired target tissue (column 2, line 45). An incorporation of stabilizer(s) and/or trafficking peptide so as to enhance transcription, translation, transcript stability, replication, and intracellular trafficking are disclosed on columns 2 and 3 as being conventional in the prior art. More importantly, Rolland teaches on columns 3 and 4 that compounds which are known to help to prolong the bioavailability of a nucleic acid, *e.g.,* protecting the nucleic acid, concentrating a nucleic acid, indirectly facilitating uptake of a nucleic acid, such as polymers, oils (a lipid based compound), surfactants can be suitably used to enhance the bioavailability of a nucleic acid.

In addition, Lunsford teaches a gene delivery method of employing a plurality of microparticles comprising a polymeric microparticles that are sized less than about 100 microns, and a plasmid DNA coding for a protein of interest such as an antigenic polypeptide, wherein the microparticles are delivered to a mucosal tissue such as vagina tissue, *e.g.,* pars 0055, Table 3, pars 0054, 0052, claims 36 and 37.

As such, it would have been obvious for one of ordinary skill in art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahasdjopoulos *et al.* One of ordinary skill in the art would have been motivated to employ the polymeric microparticles having a size of less than 100 microns in diameter of Lunsford, for example, in the complexes of Papahasdjopoulos *et al.* because Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations. One also would have been motivated to do so in order to enhance the controlled release of the lipidic:nucleic acid complexes of Papahasdjopoulos *et al.* and protect the plasmid vectors from degradation during its circulation *in vivo.*

While Rolland does not teach that the microparticle has a diameter size of 50 microns, it would have been obvious for one of ordinary skill in the art to have made, as a matter of design choice, microparticles with a diameter such so long as the microparticles could still entrap the lipidic:nucleic acid complexes of Papahasdjopoulos

et al. Note that the microparticles of different sizes of less than 100 microns are routinely made in the prior art by filtering and/or emulsion/mixing techniques, given the disclosure of Lunsford, and particularly since the size limitation does not appear to contribute any inventive feature to the invention.

It would also have been obvious for one of ordinary skill in art to employ a DNA coding for an immunogen or multiple immunogenic peptides in the DNA complexes of Papahasdjopoulos for delivery and expression at a desired target tissue such as a a mucosal tissue because Lunsford is one of many exemplified references that teach that a polymeric microparticle entrapping plasmid DNA coding for a protein of interest such as an antigenic polypeptide can be used to deliver and express such at a mucosal tissue such as vagina tissue.

One of ordinary skill in the art would have expected that such lipidic based formulation would function as to reduce plasmid degradation due to its immunogenicity and to enhance transfection activity, and that the incorporation of additional polymeric microparticles would enhance the controlled release and bioavailability of the nucleic acid/lipidic complexes. One would also have expected from the combined cited references that such enhancements including those driven by a lipid based carrier when complexed with a plasmid vector expressing an antigen would help to increase to stabilize the plasmid vector when circulated *in vivo* as the result of a controlled release from the polymeric microparticles, thereby enhancing recognition by an immune response to the expressed antigens at a target site such as a mucosal tissue.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1-4. 6, 7, 9-16, 29, 32-34, and 37, embracing a polymeric microparticle encapsulating the lipid:nucleic acid complex, are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahasdjopoulos *et al.* taken with Rolland (US Pat NO. 6,040,295), and further in view of Mathiowitz (US Pat No. 6,677,313).

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a protein or proteins of interest, and a cationic lipid/co-lipid complex. Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome.

As such, the complexes of Papahasdjopoulos *et al.* is not encapsulated in a liposome and does not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the fact that so long as the entire complex is physiologically acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Papahasdjopoulos *et al.* does not teach that the complexes can be further entrapped within polymeric microparticles that are used in the prior art to prolong the controlled release and bioavailability of a nucleic acid plasmid complex, nor does Papahasdjopoulos *et al.* teaches explicitly that an antigenic peptide or protein encoding DNA can be used for delivery and/or expression at a desired targeted tissue such as a vagina or a mucosal tissue.

However, at the time the invention was made, Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various

formulations, *e.g.,* those formulated with a carrier or stabilizer such as a cationic polymer (abstract, entire disclosure, particularly column 1 bridging column 2, column 2, second par.. , column 3, last par bridging column 4). An addition of a targeting ligand to the microparticles and/or plasmid is also taught by Rolland so as to enhance the expression of the complexed plasmid vectors at a desired target tissue (column 2, line 45). An incorporation of stabilizer(s) and/or trafficking peptide so as to enhance transcription, translation, transcript stability, replication, and intracellular trafficking are disclosed on columns 2 and 3 as being conventional in the prior art. More importantly, Rolland teaches on columns 3 and 4 that compounds which are known to help to prolong the bioavailability of a nucleic acid, *e.g.,* protecting the nucleic acid, concentrating a nucleic acid, indirectly facilitating uptake of a nucleic acid, such as polymers, oils (a lipid based compound), surfactants can be suitably used to enhance the bioavailability of a nucleic acid.

In addition, Mathiowitz teach a gene delivery method of employing a plurality of microparticles comprising a polymeric microparticles that are sized between one and ten microns, a stabilizer such as anhydride monomers, oligomers, organic dyes or metal compounds, and a plasmid DNA coding for a protein of interest such as an antigenic polypeptide, wherein the microparticles are delivered to a mucosal tissue such as vagina tissue, *e.g.,* see column 2, lines 17-56, column 4, last par., columns 7 and 8, and columns 12 and 13. Plasmid vectors including a targeting ligand is disclosed on column 19, lines 21-23.

As such, it would have been obvious for one of ordinary skill in art to employ known polymeric microparticles such as those disclosed in Mathiowitz, to entrap the lipid:nucleic acid:PEG-DSPE complexes of Papahasdjopoulos *et al.* One of ordinary skill in the art would have been motivated to employ the polymeric microparticles of Mathiowitz, or Jones, for example, in the complexes of Papahasdjopoulos *et al.* because Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations.

It would also have been obvious for one of ordinary skill in art to employ a DNA coding for an immunogen or multiple immunogenic peptides in the DNA complexes of Papahasdjopoulos for delivery and expression at a desired target tissue such as a a mucosal tissue because Mathiowitz is one of many exemplified references that teach that a polymeric microparticle entrapping plasmid DNA coding for a protein of interest such as an antigenic polypeptide can be used to deliver and express such at a mucosal tissue such as vagina tissue.

One of ordinary skill in the art would have expected that such lipidic based formulation would function as to reduce plasmid degradation due to its immunogenicity and to enhance transfection activity, and that the incorporation of additional polymeric microparticles would enhance the controlled release and bioavailability of the nucleic acid/lipidic complexes. One would also have expected from the combined cited references that such enhancements including those driven by a lipid based carrier when

complexed with a plasmid vector expressing an antigen would help to increase to stabilize the plasmid vector when circulated *in vivo* as the result of a controlled release from the polymeric microparticles, thereby enhancing recognition by an immune response to the expressed antigens at a target site such as a mucosal tissue.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 21-24, 27, and 31 are rejected under 35 USC 103(a) as being unpatentable over Papahasdjopoulos *et al.* taken with Carson (US 2003/0109469), as evidenced by Adema (US Pat No. 6,500,919).

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a protein or proteins of interest, and a cationic lipid/co-lipid complex. Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome.

As such, the microparticles of Papahasdjopoulos *et al.* is not encapsulated in a liposome and does not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the fact that so long as the entire complex is physiologically acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Papahasdjopoulos *et al.* does not teach that the DNA could code for a MHC-1 binding antigen or multiple MHC-1 binding antigens.

However, at the time the invention was made, the concept of employing a peptide or arrays of peptides known in the prior art in a plasmid expression vector for use as an immunogenic composition is taught in Carson. For example, par. 59-60 on

page 10-11 discloses that the plasmid vector can be constructed to encode an array of antigenic peptides of choice such as MHC peptides, cytokines, and/or T cell epitopes for tumor treatment, for example. As evidenced by Adema, MHC I binding peptides for use in vaccines such as treatment of a melanoma tumor are well-known in the prior art.

Thus, it would have been obvious for one of ordinary skill in the art to employ an antigenic peptide of choice such as any known MHC I binding peptide or a combination thereof in the plasmid vector taught by the primary reference. One of ordinary skill in the art would have been motivated to employ one more DNA fragments coding for peptides in the plasmid expression vector because Carson teaches on page 11 that the use of plasmid vector expressing an array of peptides of choice can be routinely made and is efficient to be used as a cocktail vaccine against more than antigens of choice, and because Adema teaches that MHC I binding peptides are effective for use in vaccine against tumor bearing patients such as melanoma patients.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 21-24, 27, 28, and 31 are rejected under 35 USC 103(a) as being unpatentable over Papahasdjopoulos *et al.* (US Pat No. 6,803,053), taken with Rolland and Lunsford, and further in view of Carson, as evidenced by Adema.

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a MHC-1 binding antigen, and a cationic lipid/co-lipid complex. Other than the limitation reciting a MHC-1 binding antigen encoding DNA for use in an expression

vector, Papahasdjopoulos *et al.* teaches the same throughout the disclosure. See column 4, lines 1-3, column 7, lines 21-31, column 8, lines 25-31. Column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome.

As such, the complexes of Papahasdjopoulos *et al.* is not encapsulated in a liposome and does not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the fact that so long as the entire complex is physiologically

acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Papahasdjopoulos *et al.* does not teach that the complexes can be further entrapped within polymeric microparticles with a diameter of less than about 100 microns that are used in the prior art to prolong the controlled release and bioavailability of a nucleic acid plasmid complex, nor does Papahasdjopoulos *et al.* teaches explicitly that a MHC-1 binding antigenic peptide or protein encoding DNA can be used for delivery and/or expression at a desired targeted tissue such as a vagina or a mucosal tissue.

However, at the time the invention was made, Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations, *e.g.,* those formulated with a carrier or stabilizer such as a cationic polymer (abstract, entire disclosure, particularly column 1 bridging column 2, column 2, second par.. , column 3, last par bridging column 4). An addition of a targeting ligand to the microparticles and/or plasmid is also taught by Rolland so as to enhance the expression of the complexed plasmid vectors at a desired target tissue (column 2, line 45). An incorporation of stabilizer(s) and/or trafficking peptide so as to enhance transcription, translation, transcript stability, replication, and intracellular trafficking are disclosed on columns 2 and 3 as being conventional in the prior art. More importantly,

Rolland teaches on columns 3 and 4 that compounds which are known to help to prolong the bioavailability of a nucleic acid, *e.g.,* protecting the nucleic acid, concentrating a nucleic acid, indirectly facilitating uptake of a nucleic acid, such as polymers, oils (a lipid based compound), surfactants can be suitably used to enhance the bioavailability of a nucleic acid.

In addition, Lunsford teaches a gene delivery method of employing a plurality of microparticles comprising a polymeric microparticles that are sized less than about 100 microns, and a plasmid DNA coding for a protein of interest such as an antigenic MHC binding antigen, wherein the microparticles are delivered to a mucosal tissue such as vagina tissue, *e.g.,* pars 0055, Table 3, pars 0054, 0052, claims 36 and 37.

As such, it would have been obvious for one of ordinary skill in art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahasdjopoulos *et al.* One of ordinary skill in the art would have been motivated to employ the polymeric microparticles having a size of less than 100 microns in diameter of Lunsford, for example, in the complexes of Papahasdjopoulos *et al.* because Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations. One also would have been motivated to do so in order to enhance the controlled release of the lipidic:nucleic acid complexes of

Papahasdjopoulos *et al.* and protect the plasmid vectors from degradation during its circulation *in vivo.*

While Rolland does not teach that the microparticle has a diameter size of 50 microns, it would have been obvious for one of ordinary skill in the art to have made, as a matter of design choice, microparticles with a diameter such so long as the microparticles could still entrap the lipidic:nucleic acid complexes of Papahasdjopoulos *et al.* Note that the microparticles of different sizes of less than 100 microns are routinely made in the prior art by filtering and/or emulsion/mixing techniques, given the disclosure of Lunsford, and particularly since the size limitation does not appear to contribute any inventive feature to the invention.

It would also have been obvious for one of ordinary skill in art to employ a DNA coding for an immunogen or multiple immunogenic peptides in the DNA complexes of Papahasdjopoulos for delivery and expression at a desired target tissue such as a a mucosal tissue because Lunsford is one of many exemplified references that teach that a polymeric microparticle entrapping plasmid DNA coding for a protein of interest such as an antigenic polypeptide can be used to deliver and express such at a mucosal tissue such as vagina tissue.

One of ordinary skill in the art would have expected that such lipidic based formulation would function as to reduce plasmid degradation due to its immunogenicity and to enhance transfection activity, and that the incorporation of additional polymeric microparticles would enhance the controlled release and bioavailability of the nucleic acid/lipidic complexes. One would also have expected from the combined cited

references that such enhancements including those driven by a lipid based carrier when complexed with a plasmid vector expressing an antigen would help to increase to stabilize the plasmid vector when circulated *in vivo* as the result of a controlled release from the polymeric microparticles, thereby enhancing recognition by an immune response to the expressed antigens at a target site such as a mucosal tissue.

With respect to the limitation of employing a MHC-1 binding peptide expressing vector in the method of Papahasdjopoulos *et al.* taken with Rolland and Lunsford., the concept of employing a peptide or arrays of peptides known in the prior art in a plasmid expression vector for use as an immunogenic composition is taught in Carson. For example, par. 59-60 on page 10-11 discloses that the plasmid vector can be constructed to encode an array of antigenic peptides of choice such as MHC peptides, cytokines, and/or T cell epitopes for tumor treatment, for example. As evidenced by Adema, MHC I binding peptides for use in vaccines such as treatment of a melanoma tumor are well-known in the prior art.

Thus, it would have been obvious for one of ordinary skill in the art to employ an antigenic peptide of choice such as any known MHC I binding peptide or a combination thereof in the plasmid vector taught by Papahasdjopoulos *et al.* taken with Rolland and Lunsford. One of ordinary skill in the art would have been motivated to employ one more DNA fragments coding for peptides in the plasmid expression vector because Carson teaches on page 11 that the use of plasmid vector expressing an array of peptides of choice can be routinely made and is efficient to be used as a cocktail vaccine against more than antigens of choice, and because Adema teaches that MHC I

binding peptides are effective for use in vaccine against tumor bearing patients such as melanoma patients.

Thus, the claimed invention was *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Ram Shukla*, may be reached at **571-272-0735.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Central Fax number, which is **571-273-8300**.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dave Nguyen
Primary Examiner
Art Unit: 1632

Da

DAVE TRONG NGUYEN
PRIMARY EXAMINER